UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER

ART UNIT	PAPER NUMBER

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/724,380	Applicant(s) MILES ET AL.	
	Examiner David Guzo	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/24/01*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,6,8-10 and 17* is/are pending in the application.

4a) Of the above claim(s) *1,2,4,5,7 and 11-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,6,8-10 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
4)☐ Interview Summary (PTO-413) Paper No(s) _____
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other

DETAILED ACTION

Claims 1-2, 4-5, 7, 11-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 5. Applicants have cancelled these claims in Paper 5.

Applicants must amend the claims to render them readable on the elected subject matter, i.e. a method of inhibiting translation of a nucleic acid containing an IRES from Hepatitis A virus, a pharmaceutical composition comprising a nucleic acid complementary to at least a portion of a Hepatitis A virus IRES which contains a Y_nX_M AUG sequence, etc.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 17 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants claim a pharmaceutical composition comprising a nucleic acid fragment complementary to at least a portion of a viral (hepatitis A) IRES which contains a Y_nX_m

AUG sequence and a pharmaceutically acceptable carrier wherein the nucleic acid fragment is present in an amount effective for inhibiting viral replication.

The test of enablement is whether one skill in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following: 1) Unpredictability of the art. The art in the area of therapeutic use of antisense oligonucleotides is extremely unpredictable. This unpredictability is manifested in areas of instability of antisense oligonucleotides *in vivo*, inability to reliably deliver the antisense drug to the disease site in the body, unpredictable and non-specific binding of the antisense drug to non-target tissues, lack of knowledge concerning the actual mechanism of action of the antisense molecules, lack of correlation between results obtained in *in vitro* or animal model studies and results obtained in humans, etc. In the instant case, the skilled artisan would need to develop protocols for selective delivery of the antisense molecules to the liver, develop protocols to render the nucleic acids resistant to nucleases present in the blood and in liver tissue, develop protocols for getting the antisense molecules to the appropriate cellular sub-component and getting the molecules in contact with the virus genome, etc. It is also noted that there are no art recognized rules governing whether a given antisense oligo will be effective. Indeed, in

previous studies, moving the target by just one or two nucleotides can greatly reduce or even eliminate antisense activity. Hoke et al. (U.S. Patent 5,585,479, issued 12/1996, see columns 15-17) notes that "...there are no rational explanations or rules that would predict active sequences." (Column 16, lines 52-53). For reviews of the unpredictability involved in the therapeutic use of oligonucleotides, see Branch, 1998, TIBS, Vol. 23, pp. 45-50; Nature Biotechnology, 1997, Vol. 15, pp. 519-524; Wallace, 1999, DDT, Vol. 4, No. 1, pp. 4-5; Pihl-Carey, 1999, Vol. 10, No. 239, pp. 1-2; Stein et al., 1994, Antisense Research And Development, Vol. 4, pp. 67-69; Stull et al., 1995, Pharmaceutical Res., Vol. 12, No. 4, pp. 465-483.

2) State of the art. The state of the art at the time of applicants' invention was nil, with no demonstrated examples of successful use of antisense oligonucleotides as pharmaceutical agents for treatment of diseases such as hepatitis A infection.

3) Number of working examples. Applicants present no working examples of the claimed invention.

4) Amount of guidance presented by applicants. Applicants present some *in vitro* data and generic guidance on methods of administering oligonucleotides to patients. However, applicants provide no guidance on how the skilled artisan would overcome the art recognized hurdles to successfully using antisense oligonucleotides to treat diseases such as hepatitis A infection in patients.

5) Nature of the invention. The invention involves a poorly developed, unpredictable area of medicine/molecular biology; the use of antisense oligonucleotides to treat hepatitis A infection.

6) Scope of the invention. The claimed invention reads on a pharmaceutical composition for treatment of hepatitis A infection.

7) Level of skill in the art. The level of skill in the art is high. However, given the unpredictable and poorly developed art, given the absence of any working examples and the lack of guidance presented by applicants, it must be considered that the skilled artisan would have had to have conducted trial and error experimentation in order to try to practice the claimed invention.

Given the above analysis of the factors which the courts have determined are critical in ascertaining whether a claimed invention is enabled, it must be considered that the skilled artisan would have had to have conducted undue and excessive experimentation in order to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 6, 8-10 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 (and dependent claims) are vague in that it is unclear what the claimed method is designed to do. The preamble of the claim recites a method for inhibiting translation of a nucleic acid containing an IRES but the last step of the claim results in the identification of nucleic acid fragments which inhibit translation of nucleic acids containing said IRES are identified. It appears that the claimed invention is designed to

be an *in vivo* testing method to identify nucleic acid sequences which can inhibit translation of nucleic acids containing an IRES element and not a method for inhibiting translation. Clarification is required.

Claim 17 is vague in that there is no definition of the symbols "Y_nX_m".

Applicants' request that a Sequence Listing be prepared for the instant application is acknowledged. A Sequence Listing will be prepared and entered into the case. However, it is noted that there are TWO paper copies of Sequence Listings in the file. One lists 26 sequences and the other lists 33 sequences. Applicants must direct the Office, by amendment, to cancel one of these paper copies of the Sequence Listing as a application cannot have more than one paper copy of the Sequence Listing.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo whose telephone number is (703) 308-1906. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Robert Schwartzman, can be reached on (703) 308-7307. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding or relating to attachments to this Office Action should be directed to Patent Analyst Zeta Adams whose telephone number is (703) 305-3291.

David Guzo
September 7, 2001

DAVID GUZO
PRIMARY EXAMINER